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10/774,325	07/12/2004	Andreas Finke	RDID01062CUS	8527

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EXAMINER	
FOSTER, CHRISTINE E	

ART UNIT	PAPER NUMBER
1641	

DATE MAILED: 06/07/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/774,325	FINKE ET AL.	
	Examiner	Art Unit	
	Christine Foster	1641	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *18 January 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-8* is/are pending in the application.

4a) Of the above claim(s) *6-8* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-5* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *12 July 2004* is/are: a)☐ accepted or b)☒ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☒ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *5/6/04*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Priority

1. Acknowledgment is made of applicant's claim for foreign priority based on an application filed in the European Patent Office on 8/10/01. It is noted, however, that applicant has not filed a certified copy of the European application as required by 35 U.S.C. 119(b).

Information Disclosure Statement

2. The information disclosure statement filed February 6, 2004 fails to comply with 37 CFR 1.98(a)(2), which requires a legible copy of each cited foreign patent document; each non-patent literature publication or that portion which caused it to be listed; and all other information or that portion which caused it to be listed.

The reference Schmidt et al. as cited on the International Search Report for the parent application PCT/EP02/08789 has been considered, which fails to teach or suggest a method of producing protein-coated microparticles with the specific limitation of a buffer of pH 10.0-12.5.

The reference DE 199 24 643 A as cited on the International Search Report for the parent application PCT/EP02/08789 was provided with an English translation for the abstract only. Therefore, only the abstract has been considered, which fails to teach or suggest the specific limitations of the instant invention.

The reference "Homobifunctional Cross-linkers" by Hermanson, G.T. has not been considered because the copy supplied did not include all listed pages and the text of other pages was partially obscured. The description of the reference also does not include the book's publication date or edition number.

Document WO 96/03652 was provided with an English translation for the abstract only. Therefore, only the abstract has been considered.

3. The listing of references in the specification is not a proper information disclosure statement. 37 CFR 1.98(b) requires a list of all patents, publications, or other information submitted for consideration by the Office, and MPEP § 609 A(1) states, "the list may not be incorporated into the specification but must be submitted in a separate paper." Therefore, unless the references have been cited by the examiner on form PTO-892, they have not been considered. The reference by Lagaly, G., et al. as listed on p. 17 of the specification has not been considered as it was not listed on the information disclosure statement.

Election/Restrictions

4. Restriction to one of the following inventions is required under 35 U.S.C. 121:

I. Claims 1-5, drawn to a method of making protein-coated polystyrene microparticles, classified in class 427, subclass 414.

II. Claims 6 and 8, drawn to a polystyrene microparticle and a test kit for performing an immunoassay test procedure, classified in class 436, subclass 533 and in class 435, subclass 287.2, respectively.

III. Claim 7, drawn to a method of detecting an analyte, classified in class 435, subclass 7.5.

The inventions are distinct, each from the other because of the following reasons:

5. Inventions I and II are related as process of making and product made. The inventions are distinct if either or both of the following can be shown: (1) that the process as claimed can be used to make other and materially different product or (2) that the product as claimed can be made by another and materially different process (MPEP § 806.05(f)). In the instant case the protein-coated microparticles of Group II can be made by a method other than that of Group I, for example, by a covalent coupling method using functionalized particles.

6. Inventions I and III are unrelated. Inventions are unrelated if it can be shown that they are not disclosed as capable of use together and they have different modes of operation, different functions, or different effects (MPEP § 806.04, MPEP § 808.01). In the instant case the different inventions are patentably distinct and have different modes of operations, different functions, and different effects. Group I is a method of making protein-coated microparticles that includes the step of combining a suspension of microparticles with a protein, while Group III is a method of detecting an analyte that includes the step of determining the amount of analyte bound to protein-coated microparticles, which is not a limitation of Group I.

7. Inventions III and II are related as process and apparatus for its practice. The inventions are distinct if it can be shown that either: (1) the process as claimed can be practiced by another materially different apparatus or by hand, or (2) the apparatus as claimed can be used to practice another and materially different process. (MPEP § 806.05(e)). In this case the immunoassay test kit of Group II can be used to practice a process other than that of Group III, for example, a solid-phase immunoassay with spectrophotometric detection that does not require the limitation of Group III of separation of a complex.

8. Because these inventions are distinct for the reasons given above, have acquired a separate status in the art because of their recognized divergent subject matter and as shown by their different classification, and the searches required for one group are not required for the others, restriction for examination purposes as indicated is proper.

9. During a telephone conversation with Marilyn Amick on May 16, 2005 a provisional election was made with traverse to prosecute the invention of Group I, claims 1-5. Affirmation of this election must be made by applicant in replying to this Office action. Claims 6-8 are withdrawn from further consideration by the examiner, 37 CFR 1.142(b), as being drawn to a non-elected inventions.

10. Applicant is reminded that upon the cancellation of claims to a non-elected invention, the inventorship must be amended in compliance with 37 CFR 1.48(b) if one or more of the currently named inventors is no longer an inventor of at least one claim remaining in the application. Any amendment of inventorship must be accompanied by a request under 37 CFR 1.48(b) and by the fee required under 37 CFR 1.17(i).

Drawings

11. The drawings are objected to as failing to comply with 37 CFR 1.84(p)(5) because they do not include the following reference sign(s) mentioned in the description: the labels "Figure 1," "Figure 2," "Figure 3," and "Figure 4" are not present in the drawings. In addition, Figure 1 contains text that is not legible: the label designating the Y-axis of the graph is not legible. Corrected drawing sheets in compliance with 37 CFR 1.121(d) are required in reply to the Office action to avoid abandonment of the application. Any amended replacement drawing sheet should include all of the figures appearing on the immediate prior version of the sheet, even if only one figure is being amended. The figure or figure number of an amended drawing should not be labeled as "amended." If a drawing figure is to be canceled, the appropriate figure must be removed from the replacement sheet, and where necessary, the remaining figures must be renumbered and appropriate changes made to the brief description of the several views of the drawings for consistency. Additional replacement sheets may be necessary to show the renumbering of the remaining figures. Each drawing sheet submitted after the filing date of an application must be labeled in the top margin as either "Replacement Sheet" or "New Sheet" pursuant to 37 CFR 1.121(d). If the changes are not accepted by the examiner, the applicant will be notified and informed of any required corrective action in the next Office action. The objection to the drawings will not be held in abeyance.

Specification

12. The disclosure is objected to because of the following informalities: the specification discloses "high-molecular proteins" (p. 6, paragraph lines 13-4; p. 7, line 22; and p. 8, line 7), which is ambiguous. The term appears to be used to refer to large proteins with high molecular weight. It is suggested that the specification be amended to read "high molecular weight proteins."

Page 10, lines 10-11 read "In the examples that follow, boldface numbers refer to the corresponding structure in the drawings." The examiner requests clarification as there do not appear to be boldface numbers in the Examples of pages 12-17 that refer to the drawings, and the drawings do not contain numbered structures.

The description of Figure 1 (p. 4, lines 9-12) does not include a description of the units of signal as shown in the Y-axis of Figure 1.

Page 15, "Example 5," line 5 discloses "reagent 2." It is unclear what this reagent comprises and to what the numeral "2" refers.

Appropriate correction is required.

Claim Rejections - 35 USC § 112

13. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

14. Claims 1-5 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

a. Claim 1 recites "...a suspension of uncoated microparticles...the suspension comprising a buffer having a pH of 10.0 to 12.5." The claim language is indefinite because it suggests that the suspension of microparticles alone, prior to combination with protein, comprises a buffer of the recited pH. The specification discloses that the pH is a critical element of the coating reaction itself (i.e., the microparticle-protein combination), which should be carried out under strongly alkaline pH conditions (p. 7, lines 9-11). It is suggested that the claim be amended to replace the phrase --"the suspension comprising a buffer having a pH of 10.0 to 12.5,"-- with --"the microparticle-protein combination comprising a buffer having a pH of 10.0 to 12.5,"--.

b. Claim 1 also recites "...incubating the combination from (a) for a period of time whereby the protein is coated by adsorption onto the microparticles...". The claim language is indefinite because it suggests that the protein is the species being coated and not the microparticles. It is suggested that the claim be amended to replace the phrase --"is coated by adsorption onto the microparticles"-- with --"is coated onto the microparticles by adsorption"--.

c. Claims 2 and 3 recites proteins in "polymerized" form. The specification provides examples of polymerized proteins (p. 6, lines 13-20) and discloses that polymerization may be achieved by chemical treatment (p. 6, lines 21-22), but does not define "polymerized." It is unclear whether polymerized proteins include only chemically

cross-linked proteins or also naturally occurring, multimeric proteins such as homodimers and the like. Furthermore, proteins are by definition polymerized, as they are polymers containing repeating units of amino acids.

d. Claim 4 recites microparticles that are "functionalized with epoxide groups" and is directed to a method of coating such particles with protein according to the method of Claim 1. However, claim 1 is directed to a method of coating particles by adsorption. The specification discloses that "Covalent coupling methods differ from adsorptive coupling methods in that the functionalized particles used in the former case have a considerably more hydrophilic surface than non-functionalized particles" (p. 1, lines 17-19). Since it is disclosed that adsorption and covalent coupling are separate methods, and that covalent coupling methods are distinguished by use of functionalized particles, the recitation of microparticles functionalized with epoxide groups in claim 4 is indefinite because it is unclear whether such microparticles are being coated by adsorption (as in claim 1) or by covalent coupling.

e. Claim 5 is indefinite due to its dependence on an indefinite claim (claim 1).

Appropriate correction is required.

Claim Rejections - 35 USC § 102

15. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

16. Claims 1-2 and 4 are rejected under 35 U.S.C. 102(b) as being anticipated by Vaynberg et al. (Vaynberg, K.A., Wagner, N.J., and Sharma, R. (2000) "Polyampholyte Gelatin Adsorption to Colloidal Latex: pH and Electrolyte Effects on Acrylic and Polystyrene Latices," *Biomacromolecules* **1**, 466-472), as evidenced by Bocquier et al. (Bocquier AA, Potts JR, Pickford AR, Campbell ID (1999) "Solution Structure of a Pair of Modules from the Gelatin-Binding Domain of Fibronectin," *Structure* 7:1451-1460).

Vaynberg et al. teach a method for producing protein-coated polystyrene microparticles that includes the steps of combining a suspension (colloid) of uncoated microparticles with a polymerized protein that is a member of a bioaffinity binding pair (gelatin), the combination comprising a buffer of pH 10, incubating the combination for a period of time whereby the protein is coated onto the microparticles by adsorption, and separating the non-adsorbed protein from the protein-coated microparticles (by centrifugation) (see p. 467, column 2, lines 30-32 and the section "Materials," lines 9-16; p. 468, column 1, lines 1-4,15-31, and Table 1; p. 469, column 1, lines 1-7, and column 2, lines 25-29; and p. 470, Figure 8). The protein gelatin is a partner of a bioaffinity binding pair as it binds fibronectin (see Bocquier et al., p. 1451, column 2, lines 1-10) and the polystyrene latex used by Vaynberg et al. is characterized as hydrophobic (p. 469, lines 25-27).

17. Claims 1-2 and 4 are rejected under 35 U.S.C. 102(b) as being anticipated by Jolley et al. (Jolley ME, Wang CH, Ekenberg SJ, Zuelke MS, Kelso DM (1984) "Particle

concentration fluorescence immunoassay (PCFIA): a new, rapid immunoassay technique with high sensitivity," *J Immunol Methods* **67**:21-35) as evidenced by Rembaum et al. (US Patent No. 3,957,741).

Jolley et al. teach a method for producing protein-coated polystyrene microparticles comprising the steps of combining a suspension of uncoated microparticles with a polymerized protein that is a member of a bioaffinity binding pair (immunoreactive species, e.g. antigen), the combination comprising a buffer of pH 10, incubating the combination for a period of time whereby the protein is coated onto the microparticles by adsorption, and separating the non-adsorbed protein from the protein-coated microparticles (by centrifugation) (see p. 23, lines 30-32; p. 25, lines 1-5; p. 26, lines 10-15; p. 27, lines 10-14; p. 28, Table I). Polystyrene latex has a hydrophobic surface as evidenced by Rembaum et al. (column 2, lines 3-4).

Although Jolley et al. do not specifically recite that the protein is coated by adsorption, this would inherently be the case when coating non-functionalized polystyrene microparticles at pH 10.

18. Claims 1-2 and 4 are rejected under 35 U.S.C. 102(b) as being anticipated by Ortega Vinuesa et al. (Ortega Vinuesa, J. L.; Galvez Ruiz, M. J.; Hidalgo-Alvarez, R. (1996) *Langmuir* **12**:3211-3220).

Ortega Vinuesa et al. teach a method for producing protein-coated polystyrene microparticles comprising the steps of combining a suspension of uncoated microparticles, which may be hydrophobic, with a polymerized protein that is a member of a bioaffinity binding pair ($F(ab')_2$;), the combination comprising a buffer of pH 10,

incubating the combination for a period of time whereby the protein is coated onto the microparticles by adsorption, and separating the non-adsorbed protein from the protein-coated microparticles (by filtration) (see p. 3211, section 2.1, lines 1-3; p. 3213, section 2.2, section 2.3, lines 1, 10-16, and 22-25 in particular; and p. 3213, column 2, lines 9-14 and lines 34-38 in particular).

Claim Rejections - 35 USC § 103

19. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

20. The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

21. Claims 1-2 are rejected under 35 U.S.C. 103(a) as being unpatentable over Amiral et al. (US Patent No. 5,175,112) in view of Steel et al. (US Patent No. 5,858,648). Amiral et al. teach a method for producing protein-coated polystyrene microparticles substantially as claimed. The method includes the steps of combining a suspension of uncoated microparticles with a protein that is a member of a bioaffinity

binding pair ("immunological substance"), the combination comprising a buffer of pH 10, incubating the combination for a period of time whereby the protein is coated onto the microparticles by adsorption (see column 6, lines 31-35, column 7, lines 1-11, 49-51, and 59-62; column 8, lines 19-30; and column 13, Example 5, lines 9-20). Amiral et al. include the step of rinsing the protein-coated microparticles (column 15, lines 18-19), but fail to specifically recite that the non-adsorbed protein is thereby separated from the protein-coated microparticles.

However, Steel et al. teach a method for producing protein-coated polystyrene microparticles by adsorption that includes the steps of combining uncoated microparticles with a polymerized protein that is a member of a bioaffinity pair (toxoplasma and rubella antigens) in a suspension comprising a buffer of pH 9.6 and *separating the non-adsorbed protein from the protein-coated microparticles by centrifugation* (see column 6, lines 40-42 and column 11, Example 1, lines 28-49). Steel et al. teach that the centrifugation of the coated microparticles in removing excess (i.e., unbound) antigen (column 11, lines 45-49).

Therefore, it would have been obvious to one of ordinary skill in the art at the time of the invention to include the centrifugation step as taught by Steel et al. in the method for producing protein-coated polystyrene microparticles of Amiral et al. because the Steel et al. teach the benefit of centrifugation in removing excess antigen from the reaction mixture.

22. Claim 3 is rejected under 35 U.S.C. 103(a) as being unpatentable over Jolley et al. in view of Tischer et al. (US Patent No. 5,061,640). Jolley et al. is as discussed

above, which fails to teach a method for producing a method for producing protein-coated polystyrene microparticles where the protein is a polymerized streptavidin.

Tischer et al. teach a process for the preparation of a protein for binding to an insoluble carrier material (see column 2, lines 25-34 and column 4, lines 19-38). In particular, Tischer et al. teach polymerizing streptavidin by cross-linking, coupling the cross-linked streptavidin to a specifically bindable substance, and adsorbing the protein to polystyrene (column 8, Example 2, lines 38-42; and column 9, part (d), lines 9-10). Tischer et al. further teach that polymerizing proteins, including streptavidin, has the effect of increasing the molecular weights of the proteins (column 3, lines 32-43), which results in improved adsorption to the insoluble carrier material (see column 2, lines 35-37).

Therefore, it would have been obvious to one of ordinary skill in the art at the time of the invention to employ polymerized streptavidin, as taught by Tischer et al., in the method for producing protein-coated microparticles of Jolley et al., because Tischer et al. teach that polymerization of streptavidin results in improved adsorption to insoluble carriers, including polystyrene, and that this binding is stable with regard to detergents.

23. Claim 5 is rejected under 35 U.S.C. 103(a) as being unpatentable over Jolley et al. in view of Bangs (Bangs, L.B. (1996) "New developments in particle-based immunoassays: introduction," *Pure & Appl. Chem.* **10**:1873-1879). Jolley et al. is as discussed above, which fails to teach microparticles that have a magnetizable core.

However, Bangs teaches microparticles that have a magnetizable core (superparamagnetic particles and magnetic microspheres; see p. 1873, "Introduction," lines 1-4 and p. 1876, "Superparamagnetic Particle Based Assays") and their utility in fast and easy separation of solid and liquid phases.

Therefore, it would have been obvious to one of ordinary skill in the art at the time of the invention to include the microparticles having a magnetizable core as taught by Bangs in the method for producing protein-coated polystyrene microparticles of Jolley et al. because Bangs teaches the convenience of such microparticles in the fast and easy separation of solid and liquid phases in various assay types, including RIA, ELISA, and immunoradiometric assays.

Conclusion

24. No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Christine Foster whose telephone number is (571) 272-8786. The examiner can normally be reached on M-F 8:30-5.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Long Le can be reached on (571) 272-0823. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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